New Computer-Based Tools for Empiric Antibiotic Decision Support

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ABSTRACT

Since 1995 we have been developing a decision-support model, called Q-ID, which uses a series of infectious disease knowledge bases to make recommendations for empirical treatment or to check the appropriateness of current antibiotic therapy. From disease manifestations and risk factors, a differential diagnosis for the patient is generated by a diagnostic medical expert system. The resulting probability of each disease is multiplied by the expected benefit in improved mortality and morbidity from optimal antibiotic treatment of each disease. To generate empirical treatment recommendations, site-specific data on sensitivity to antibiotics of each organism is used as an estimate of the likelihood of achieving maximum benefit for each disease on the patient's differential. Combining this data with drug and patient specific factors, the model recommends the antibiotic(s) most likely to produce the optimal benefit in this patient with the least risk and expense. In this paper the model is described, excerpts from each of the knowledge bases are presented, and performance of the model in a real case is shown for illustration.

INTRODUCTION

Current literature contains evidence that computer programs have proved to be effective in reducing hospital acquired infections by assisting physicians in selecting the best antibiotics for patients with suspected or confirmed infections [1-4]. Evans, et.al, demonstrated that some nosocomial infections are preventable or minimized with appropriate empiric antibiotic treatment using a computer-based antibiotic assistant program. The proven utility and the need for a modular and portable system led to our research and development in this area. Our work is focused on the empiric phase of antibiotic treatment which starts when the physician first detects evidence of infection but pathogens are still unknown. Infectious disease specialists spend as much as 50% of their time doing empiric consults to help minimize antibiotic misuse [5].

The antibiotic of choice for the treatment of an infection is a multifactorial process which includes site of infection, intrinsic activity of the drug, activity of the drug at the site of infection, toxicity, and cost as in the "Evans" model[2]. However, early treatment choices are also complicated by incomplete diagnostic information and expert knowledge about morbidity and mortality risk for treated versus untreated patients. For example, empiric therapy may include an antimicrobial that treats a less likely but life threatening disease process until further data "rules out" the diagnosis. In this paper, we describe the development and on-going evaluation of decision support software and knowledge bases designed to assist with the empiric antibiotic choices made by physicians.

MODEL DESIGN

Perhaps the central challenge in the clinical care of a sick patient is the ability to recognize when it is appropriate to intervene and what kind of intervention will improve the quality of life for that patient. The object of the decision support system discussed in this paper is to help the health care provider recognize opportunities for appropriate intervention, defined as a circumstance where intervening in the natural course of events underway in a particular patient would result in more good days of life for that patient. Recognition of an intervention opportunity must be based on several types of knowledge as well as accurate and timely observations of the patient.

Knowledge Bases used by the Model:

1. relation of data such as symptoms, physical findings, risk factors and test results, to disease manifestations (probability of each disease explaining this patient's clinical profile),
2. expected course of disease in terms of mortality and morbidity (MM) if untreated,
3. expected course of disease in terms of MM if treated with optimal intervention,

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4. the fraction of patients with each disease expected to respond to each intervention under consideration,
5. cost of each intervention.

Our working antibiotic decision support model, called Q-ID, uses these knowledge bases in its calculations. Q-ID first takes into account the likelihood that the patient is infected with a particular organism. Using the object libraries from a diagnostic expert system, Iliad [6], the posterior probabilities of diseases are calculated based on risk factors such as patient's location and disease manifestations at the time Q-ID is invoked. The portion of the extensive Iliad knowledge base that Q-ID uses consists of diagnoses for 150 infectious diseases. The Iliad knowledge frames which are associated with these diagnoses include many intermediate decisions. A sample Iliad frame is shown below:

Title: Cystitis; enteric gram negative	Category: UTI	
a priori: 0.005 (inpatient population)		
A. Demographic: age is == years old	Sensitivity	1-Spec.
>=0	.10	.10
>=5	.01	.16
>=16	.60	.24
>=41	.05	.25
>=66	.25	.25
B. Demographic: Gender female	.95	.50
C. **Cystitis**	.99	.007
D. **Urine positive enteric gram neg. org**	.99	.05
E. Urine gram stain pos. gram neg. bacilli	.80	.10

The frame above uses information collected from other nested diagnostic frames (shown as bolded and underlined) such as the following Cystitis frame. Other nested frames within the Cystitis frame define risk factors, signs, symptoms, and lab findings of UTI and so forth.

Title: Cystitis	Category: UTI	
a priori: 0.03 (inpatient population)		
A. **At risk for UTI**	.95	.80
B. **Nonspecific acute bacterial infection: signs & symptoms**	.25	.05
C. **Signs & symptoms of septic shock**	.01	.005
D. **Signs & symptoms of UTI**	.90	.05
E. **Lab findings of UTI**	.85	.10
F. Pelvis, and back symptoms: flank pain	.001	.01
G. Examination of the trunk/back and pelvis: tenderness to palpation at costovertebral angle (CVA)	.001	.01
H. General appearance: patient looking acutely ill	.0005	.01

Findings used by Iliad are defined in Q-ID's dictionary which currently consists of 2,043 dictionary terms - sufficient to support the clinical decisions under consideration. These terms are categorized as follows: 1,221 microbiology and virology lab terms, 213 history terms, 162 disease names, 117 general chemistry terms, 83 physical exam terms, 70 hematology terms, 31 radiology terms, and a few other assorted terms.

In our model, the potential benefit achievable by optimal treatment of each disease is measured by the expected difference in mortality (represented as a probability of dying times the actuarial life expectancy of the patient) and morbidity (of both short-term and long-term sequelae) treated and untreated. A table has been created that contains for each disease the expected difference in morbidity and mortality, expressed as the difference in good days of life saved (GDS), attributable to optimal treatment of each disease. This table contains morbidity and mortality (MM) data on approximately 150 infectious diseases. The numbers used in this table are based largely on expert opinion and data from the literature when available. A sample of the data contained in the MM table:

Morbidity & Mortality Table

Disease	Mortality with Rx	Mortality without Rx	Acute Morb. with Rx	Acute Morb. without Rx	Days of Acute Morb. with Rx	Days of Acute Morb. w/o Rx	Long Term Sequelae with Rx	Long Term Sequelae w/out Rx	Days morb Long Term	Morbidity of Sequelae
Bacteremia; serratia	0.2	0.39	0.8	0.9	21	60	0.01	0.09	900	0.4
Bacteremia; shigella	0.2	0.39	0.8	0.9	21	60	0.01	0.09	900	0.4
Cellulitis; staph aureus	0.001	0.15	0.3	0.4	10	30	0.001	0.01	60	0.2
Cellulitis; group a streptococcus	0.009	0.2	0.4	0.6	10	30	0.01	0.09	90	0.4
Cystitis; candida	0.00009	0.001	0.001	0.0015	3	14	0.0001	0.001	90	0.3
Cystitis; citrobacter	0.0001	0.001	0.001	0.0015	3	14	0.0008	0.001	90	0.3
Cystitis; escherichia coli	0.0001	0.001	0.001	0.0015	3	14	0.0008	0.001	90	0.3

Q-ID % Susceptibility Table

Organisms / Antibiotics Urine Hospital-wide	Amikacin	Ampicillin	Cefuroxime	Ceftazidime	Cefazolin	Gentamicin	Ofloxacin
Enterobacter aerogenes	100	0	56	78	0	100	98
Enterobacter cloacae	98	0	50	84	0	97	93
Escherichia coli	99	63	100	100	94	97	99

Once the optimal GDS has been calculated across all likely diagnoses, the "site-specific" susceptibility table is invoked. This table contains sensitivity of each organism to antibiotics that will have optimal effect on each disease or the fraction of the optimal effect. The Q-ID susceptibility table consists of percentages of susceptibility and resistance testing of 268 unique organisms against 95 antibiotics, a portion of which is shown above in the Q-ID Susceptibility Table. This data was obtained from the University of Utah laboratory system and is catalogued by culture type, hospital location, date and organism isolated. Epidemiology rules sort the culture results into likely "true positives" and same episodes so that the susceptibility results are not biased by multiple cultures during a single infectious episode nor probable contaminant [7].

The percentages for each antibiotic are then multiplied by the maximum GDS for each disease to determine effectiveness of a given drug against the most likely diseases. Q-ID then creates a list of antibiotics, ordered by potential benefit in the treatment of a patient suspected to have an infection before culture results are available (it can also be used after culture results are available). The potential benefit of each antibiotic is measured by the difference in expected morbidity and mortality expressed as Good Days of life Saved (GDS) by each antibiotic.

The expected gain measured in GDS from each antibiotic for each likely disease identified by Iliad is weighted by the probability of each disease and summed across all diseases. The antibiotics that cover the largest fraction of the potential gain will be recommended to the physician. After the GDS has been calculated, patient specific factors (allergies, renal and hepatic function, height, weight), drug specific factors (toxicity and cost), and disease specific factors (route of administration, site/drug penetration) are evaluated to determine the top therapeutic choices. The following case scenario illustrates how Q-ID works.

CASE SCENARIO (Q-ID)

A 78 year old male patient was admitted to the hospital 3 days ago after slipping on the ice and breaking his hip. The hip was surgically repaired the next day. He is now mildly disoriented and found to have a temperature of 100.5° F, pulse of 104 bpm, respiratory rate of 20 rpm, and blood pressure of 110/60 mmHg. An intravenous and Foley catheter are in place.

The patient's laboratory results are as follows: WBC: 9,000/$_{mm}^{3}$, Hgb: 9.7 gm/dL, Hct: 28%, BUN: 32 mg/dL, Creatinine: 1.2, Urine Analysis: RBC: 294/HPF, Nitrate: Positive, WBC: 15/HPF. Radiology results indicate: Femoral neck fracture, Normal chest PA & LAT on Day 1; Decreased lung volumes with possible atelectasis and no infiltrate/signs of pneumonia seen on chest PA & LAT x-rays on Day 3; and colonic ileus noted on an abdominal series performed on Day 4.

Q-ID passes this patient information to Mosby's Iliad[6] object library component to calculate a differential diagnosis.

Disease - Organism	Probability
Urinary tract infection - *E. coli*	.42
Urinary tract infection - *K. pneumonia*	.27
Bacteremia - *E. coli*	.25
Urinary tract infection - *P. mirabilis*	.15
Surgical site infection - *S. aureus*	.10
Surgical site infection - *S. pyogenes*	.09
Pneumonia, nosocomial - *E. cloacae*	.09
Pneumonia, nosocomial - *E. coli*	.09
Bacteremia - *S. aureus*	.08

Q-ID then determines the local pattern of antimicrobial susceptibility for the organism in the differential diagnosis, for example, E. coli (1,700 isolates from 1,094 infectious episodes).

E. Coli Antimicrobial	% susceptible of nosocomial isolates
Ceftazidime	100
Cefuroxime	100
Ofloxacin	99
Gentamicin	97
Cefazolin	94
TMP/SMX	92
Ampicillin	63
Vancomycin	0

Q-ID uses the mortality, morbidity and life expectancy tables to calculate the GDS (Good Days of Life Saved) for each appropriate antibiotic. These antimicrobials, if present on hospital formulary, are ranked by efficacy and then by toxicity and then by cost. Potential GDS not covered by the leading antimicrobial is then considered for a second agent.

Antibiotic	GDS	% of max GDS	Toxicity	Scaled Cost
Ceftazidime	3855	88%	2	$23.70
Ampicillin & Gentamicin	3224	74%	5	$3.51
Cefuroxime	3200	73%	2	$22.32
Ofloxacin	2650	61%	2	$5.28
Cefazolin	2400	55%	2	$5.49
Gentamicin	2335	53%	2	$0.33
TMP/SMX	2224	51%	5	$2.76
Vancomycin	525	12%	4	$12.80

Ceftazidime is therefore ranked #1 and will save 88% of the potential GDS. A "Recommend" button will allow physicians to narrow this list to just those antibiotics that have equivalent GDS scores (have scores within 15% of top choice). Upon request, Q-ID can then make patient-specific recommendations based on allergies, renal and hepatic function, and disease process. If the physician selects an antibiotic from the "recommended" list, a detailed dosing recommendation is displayed. See below:

Present information suggests a probable urinary tract infection with the possibility of bacteremia or wound infection.

Recommend: **Urine culture**
Blood culture
Examination of wound
Ceftazidime 1.0gm Q 8° IV

This patient was found to have a urinary tract infection and bacteremia with E. coli. His attending surgeon had started Cefazolin based on his anecdotal experience. The E. coli isolated was similar to other nosocomial E. coli isolates in this hospital and turned out to be resistant to Cefazolin. Initial coverage with recommended antibiotic would have probably reduced this patients recovery time and decreased his stay in the hospital.

Current Evaluation

The antibiotic adviser expert system, Q-ID, is now undergoing a formative evaluation. We have begun by selecting 50 charts from medical records of patients who have had an infectious disease episode during their hospital stay. The pertinent clinical information (relevant to the infectious episode) is gleaned from the paper chart by an expert abstractor and entered into a database. Care is taken to preserve the chronological sequence of events. Then each patient case is opened in our Q-ID editing and testing program. The system's diagnoses and recommendation at each step along the hospital course are compared to the diagnoses and recommendation of the domain experts at the same point. When modifications are required, changes are made to the software, table content, or both until the model behaves accurately and predictably. At the point where the model stabilizes, we will "freeze" the program and run it against another set of 50 patients in an evaluative phase. Experts, separate from the development team, will review abstracted cases and a blinded comparison will be performed against Q-IDs recommendation.

Once the model stabilizes and is validated, Q-ID will be interfaced to an existing operational patient care system at the University of Utah. We also plan studies to determine how well Q-ID performs as compared with various levels of physician expertise (medical resident, general practitioner, infectious disease expert).

DISCUSSION

Our group has attempted to add additional utility to contemporary antibiotic assistant paradigms. By using Iliad's diagnostic object library to suggest working hypotheses at the onset of nosocomial infections, we hope to narrow the plausible diagnoses. In addition, we have introduced a new knowledge source by using morbidity and mortality estimates to introduce an "urgency" factor into the decision process. Since there is some inherent subjectivity contained in the estimates used in the morbidity and mortality tables, we will be conducting sensitivity testing on how the quality of the M&M information affects the conclusions reached by Q-ID.

The various testing and validation efforts currently underway will hopefully serve to measure the degree to which these concepts add value to contemporary antibiotic assistant paradigms.

In building Q-ID, we have incorporated the flexibility that will enable the use of site-specific knowledge upon which to calculate the likelihood of diagnoses, organisms, and sensitivities to antibiotics. This will become an important factor as this technology moves from the University of Utah to other institutions. For example, since antibiogram data is specific to a given hospital, Q-ID tools can incorporate years worth of local data when it is available. Portability of Q-ID to other sites will also be enhanced by our model that is formula based, where recommendations are expressed in terms of good days of life saved (GDS) for each antibiotic. This minimizes the inherent complexity of establishing and maintaining a convoluted rule-based system.

With few exceptions, clinical decision support systems have had limited positive impact on the daily operation of clinical care. Because of this we believe Q-ID must be seamlessly integrated into the workflow of patient care. Once this is accomplished we hope that Q-ID will assist the physician in making decisions regarding appropriate intervention avoiding unnecessary, potentially harmful, or sub-optimal treatment with antibiotics.

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